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Brain Anomalies, Retardation of Mentality and Growth, Ectodermal Dysplasia, Skeletal Malformations, Hirschsprung Disease, Ear Deformity and Deafness, Eye Hypoplasia, Cleft Palate, Cryptorchidism, and Kidney Dysplasia/Hypoplasia (BRESEK/BRESHECK): New X-Linked Syndrome?

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Two half brothers (maternally related) had a similar syndrome of microhydrocephaly in both brothers and dilatation of the spinal canal with fusion of thalami in one brother. Primordial growth delay was noted in both brothers, with severe mental retardation in the surviving brother. Both had ectodermal dysplasia with scaling, hyperkeratosis, and generalized alopecia, but normal sweat and sebaceous glands. Skeletal anomalies included hemivertebrae with abnormal segmentation in one and scoliosis with polydactyly in the other. Ears were apparently low set, large, and protruding, with mixed hearing loss in the brother who survived. Eye anomalies included maldevelopment of one eye in Patient 1 and small optic nerves more noticeable on one side in Patient 2. Both had cryptorchidism and dysplastic/hypoplastic kidneys of varying severity that resulted in the early postnatal death of one sib. Manifestations present in only one or the other sib included submucous cleft palate, aganglionosis of the rectum and colon, agenesis of one testicle, and single umbilical artery. This syndrome has not been described previously and may be due to an X-linked mutation. The acronym BRESEK reflects the common findings, whereas BRESHECK denotes all manifestations of both patients: brain, retardation, ectodermal dysplasia, skeletal deformities, Hirschsprung disease, ear/eye anomalies, cleft palate/cryptorchidism, and kidney dysplasia/hypoplasia. In addition to an X-linked mutation, a contiguous gene deletion or maternal mosaicism of an autosomal dominant gene must be considered. Am. J. Med. Genet. 68:386–390, 1997.

KEY WORDS: alopecia; renal dysplasia; Hirschsprung; clefting; eye hypoplasia

INTRODUCTION

We present a previously apparently undescribed syndrome with a unique pattern of malformations.

CLINICAL REPORTS

Patient 1

The patient was born to an 18-year-old gravida 1 mother and a 19-year-old father, both healthy white individuals without consanguinity. The pregnancy was complicated by intrauterine growth retardation with oligohydramnios, and delivery was premature at 32 weeks gestation due to uncontrolled contractions. Birth weight was 990 g (3rd centile) with a head circumference (OFC) of 25 cm (<10th centile). Multiple congenital malformations were noted at birth including acrocephaly; microphthalmic right eye; beaked nose; apparently low-set, posteriorly angulated, large ears; micrognathia

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without cleft palate; webbed neck; hypoplasia of the right chest; scoliosis; postaxial polydactyly of the right hand; bilateral talipes calcaneus; and multiple flexion contractures with a dislocated left hip. Also noted were lamellar desquamation with diffuse scaling, most notably on the scalp, and generalized alopecia of the scalp, eyebrows, and eyelashes. The patient died of severe respiratory distress 6 hours after delivery. An autopsy revealed enlarged lateral cerebral ventricles, absence of the septum pellucidum, and fusion of the thalami. The central canal of the thoracic spinal cord was dilated. The right eye was present only as a "bud." The lungs were hypoplastic with pneumothorax. The kidneys were dysplastic and multicystic bilaterally without ureters. The bladder was hypoplastic with no external orifice. Both testes were undescended but normal in architecture. Only one umbilical artery was present. Microscopy demonstrated marked epidermal hyperkeratosis with hyperkeratinized hair follicles. There was a paucity of hair follicles on several sections, but eccrine gland density was normal. The epidermal changes were consistent with a form of ectodermal dysplasia. A histologic review of rectal sections demonstrated normal ganglion cells.

Results of cytogenetic studies performed in 1978 using lung and skin fibroblasts were normal (46,XY).

Patient 2

The propositus (Fig. 1) was the half brother of patient 1 (maternally related). This mother and father were 27-year-old healthy white individuals without consanguinity. The pregnancy was full term, and delivery was uneventful with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Birth weight was 2,230 g (3rd centile), length was 43 cm (<3rd centile), and OFC was 30.5 cm (<10th centile). Multiple congenital anomalies included asymmetric head with plagiocephaly and flattening of right occiput, protruding and apparently low-set ears, and submucous cleft of the soft palate. The neck was short. The left testicle was undescended. Eye examination showed small and oval-shaped optic nerves more noticeable on the right side. A generalized alopecia was present with absence of scalp hair, eyebrows, and eyelashes. The skin was dry and scaly. Hyperkeratotic spiny lesions were prominently present in a follicular pattern specifically on the scalp and trunk. The umbilical cord was normal. Complex neonatal seizures were controlled with multiple anticonvulsants. An electroencephalogram (EEG) showed an abnormal pattern of intermittent sharp waves of the left parietal lobe, and magnetic resonance imaging (MRI) of the brain demonstrated thinning of the corpus callosum with dilatation of ventricles. Computed tomography (CT) scan documented no evidence of craniosynostosis, but there was mild deformity of the skull with facial bones protruding on the right. Brain stem evoked response examination revealed bilateral mixed hearing loss, particularly in the high frequencies. A bone survey demonstrated an abnormal segmentation of the third to fifth ribs on the right, balanced hemivertebrae in the two lowest thoracic and first lumbar vertebral bodies. A renogram and renal ultrasound failed to detect any renal activity or renal structure on the left side consistent with hypoplasia/agenesis of that kidney. A voiding cystourethrogram showed an extremely small bladder and complete vesicoureteral reflux on the right with a mild degree of caliectasis, pyelectasis, and ureterectasis. No clinical signs of renal failure were present. Scalp biopsy demonstrated a reduced number of hair follicles and units. Of the hair follicles present, most appeared to be abnormal, with evidence of pathologically excessive keratinization (Fig. 2). Sweat glands were present (Fig. 3). The sebaceous glands were not as prominent as expected for that age.

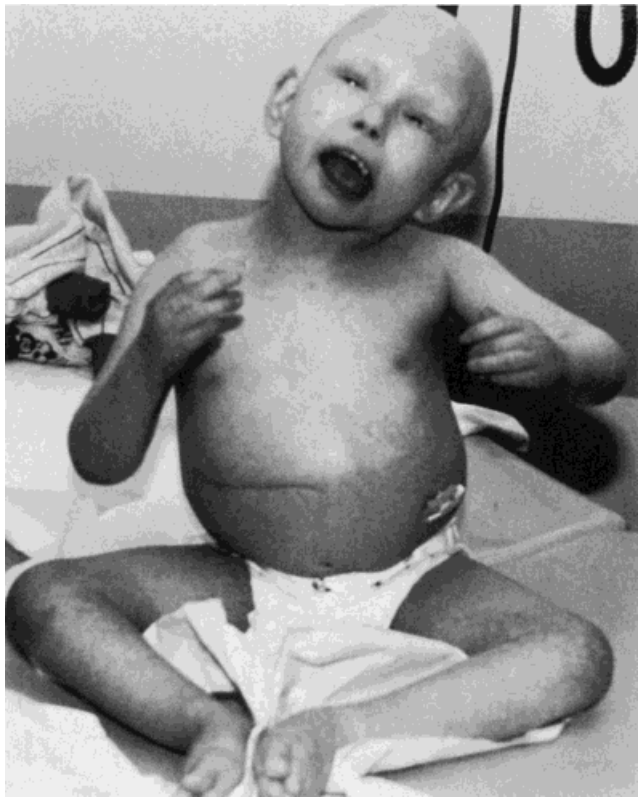

Fig. 1. Patient 2, showing general alopecia, plagiocephaly, right microphthalmia, apparently low-set and large ears, gastrostomy, and abdominal scars.

Plasma amino acids, urine organic acids, and reducing substances were normal. Cytogenetic studies analyzing 20 metaphase peripheral blood cells, using G-banding, showed no numerical or structural chromosomal abnormality. The karyotype was 46,XY.

At 5 weeks of age the patient developed intestinal obstruction, and the diagnosis of Hirschsprung disease was confirmed by rectal biopsy demonstrating nerve fiber hypertrophy and an absence of ganglion cells. Pull-through of the normal transverse colon with closure of colostomy was performed at age 5 years, along with an explorative laparotomy that confirmed absence of the left testicle. A Nissen fundoplication to control gastroesophageal reflux was successful.

Reexamination at 7 years of age demonstrated marked developmental and somatic growth delay. The patient was able only to babble, sit, and crawl; his developmental age was 9 months. Seizures were controlled with

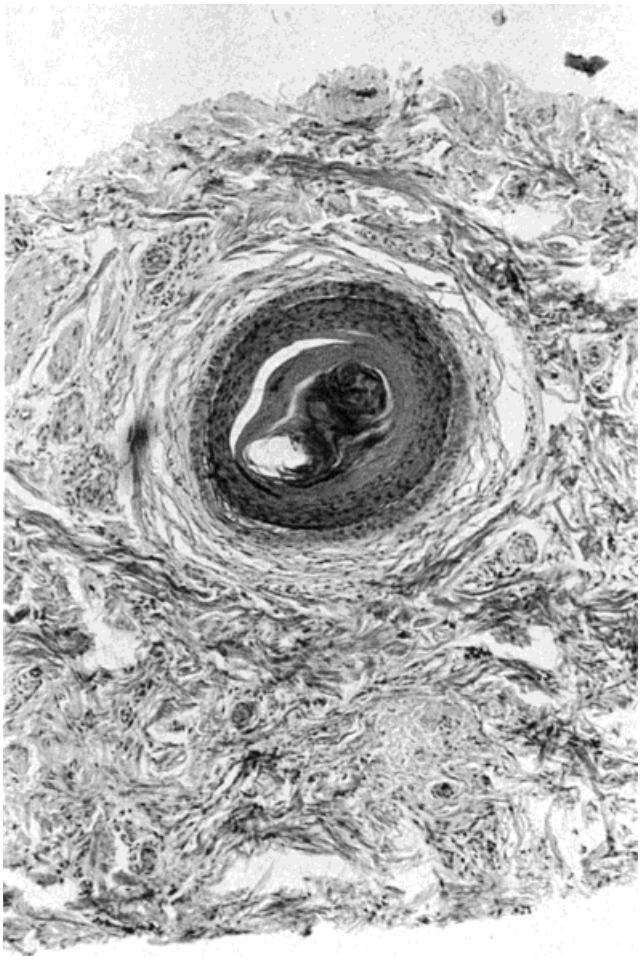

Fig. 2. Scalp skin biopsy specimen from patient 2, hematoxylin and eosin stained, showing sparse hair follicles and abnormal hyperkeratinization of the follicle present.

valproate. Eucerin cream was frequently applied to his dry skin that had been occasionally infected with yeast. A repeat karyotype at high resolution (>550 bands) was normal. His OFC was 45.25 cm (<5th centile), length was 90 cm (<5th centile), and weight was 12 kg (5th centile). His head was plagiocephalic with a prominent right side. There was no scalp hair, eyelashes, or eyebrows. There was corneal thickening and a smaller palpebral fissure on the right. The inner canthal distance was 3.2 cm (+1 SD), and the outer canthal distance was 9 cm (−1 SD). Teeth were normal in number and shape. The ears were apparently low set and protruding, measuring 6 cm (+2 SD), with incomplete outer helix formation. The neck was short. The chest was normal, with normal heart and lung sounds. The patient had a gastrostomy and no organomegaly. No scoliosis was found. He had a normal penis and a descended testicle on the right. His hands were small, with total length of 10.3 cm (<3rd centile) and tapering fingers. The feet had a rocker bottom shape with the second toe overriding the third on both feet. The skin was mildly scaly with atopic dermatitis of groin and

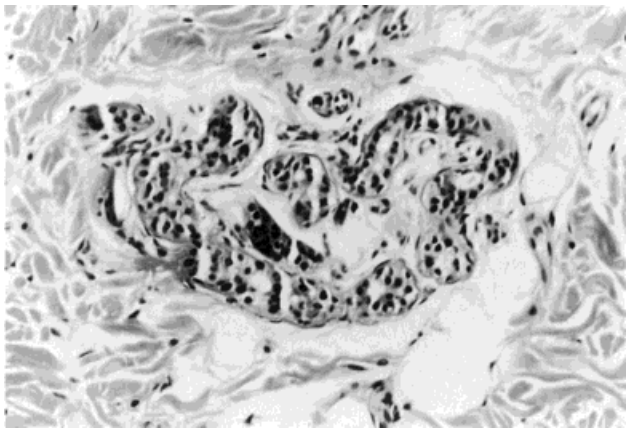

Fig. 3. Skin biopsy showing normal sweat glands.

flexures. The spiny hyperkeratotic lesions were still present primarily on the scalp, upper back, and shoulders, but were less noticeable compared with the initial examination. The fingernails had a yeast infection. Neurologically, muscle tone and normal reflexes were reduced.

Family History

No information was available regarding the paternal side of Patient 1, and information was noncontributory on the paternal side of Patient 2. The latter had a 9-year-old healthy full brother. The mother had a brother who died a few hours after delivery of undefined cause, with a reported failure of growth but with no other history of anomalies similar to those of the propositus. The maternal grandmother had a colostomy at the age of 50 years due to an abnormal rectal sphincter, with no evidence for Hirschsprung disease.

DISCUSSION

We present two half brothers (maternally related) who had a similar pattern of malformations and suggest that it comprises a "new" syndrome. The acronym BRESEK reflects the common manifestations, whereas BRESHECK denotes the broadest spectrum seen in one or both patients: brain, retardation, ectodermal dysplasia, skeletal deformities, Hirschsprung disease, ear/eye anomalies, cleft palate/cryptorchidism, and kidney dysplasia/hypoplasia and reflux.

Brain anomalies included hydromicrocephaly in both brothers and dilatation of the spinal canal with fusion of thalami in one brother. Retardation was evidenced as primordial growth delay in both, with continuous failure to thrive in the surviving brother. The latter had profound mental retardation despite early intensive infant stimulation. Both had an ectodermal dysplasia with scaling, hyperkeratosis, and generalized alopecia, but normal sweating with normal teeth in the older boy. Recurrent fingernail infection in the latter could be attributed to his habitual digito-oral manipulation, as his toenails were normal and had never been infected. Skeletal anomalies included plagiocephaly, hemivertebrae

TABLE I. Phenotypic Findings of Reported Patients With Partial Similarity to Our Patients

	Goldberg and Shprintzen [1981]		Hurst et al. [1988]			Brunoni et al. [1983]	Santos et al. [1988]	Sanyanusin et al. [1995]	Present study	
	Patient 1	Patient 2	Patient 1	Patient 2	Patient 3				Patient 1	Patient 2
Brain malformation	+[a]	+[a]	+[c]	+[a]	−	−	?	−	+[a,i]	+[a]
Microcephaly	+	+	+	+	+	+	?	−	+	+
Mental retardation	+	+	+	+	+	+	+	−	?	+
Growth delay	+	+	−	+	−	−	?	+	+	+
Deafness	?	?	−	?	?	?	+	−	?	+
Generalized alopecia	−	−	−	−	−	−	−	−	+	+
Ectodermal dysplasia	−	−	−	−	−	−	−	−	+	+
Eye malformations	−	−	+[d]	?	+[d]	−	−	+[h]	+[j]	+[k]
Cleft lip/palate	+	+	?	?	?	+	−	−	−	+
Kidney malformations	−	−	?	+[e]	?	−	+[g]	+[e,g]	+[g]	+[e,g]
Cryptorchidism	+		?	?		?	?	−	+	+[l]
Hirschsprung disease	+	+	+	+	+	+	+	−	−	+
Skeletal anomalies	+[b]	−	?	?	?	+[f]	−	−	+[b,f]	+[m]
Polydactyly	−	−	−	?	−	−	+	−	+	−
Sex	M	F	M	M	F	M	M	M	M	M
Normal karyotype	+	?	+	?	+	+	+	+	+	+

? not evaluated.
[a] Ventricular dilatation.
[b] Scoliosis.
[c] White matter irregularity.
[d] Coloboma of iris.
[e] Ureteral reflux.
[f] Pectus excavatus, talipes calcaneous.
[g] Hypoplasia/agenesis of kidney.
[h] Bilateral optic coloboma.
[i] Dilatation of spinal canal and thalamus fusion.
[j] Agenesis of one eye.
[k] Small optic nerves, more on one side.
[l] Agenesis of one testicle.
[m] Abnormal segmentation, hemivertebrae, plagiocephaly.

with abnormal segmentation in one and scoliosis with polydactyly in the other. The ears were large and protruding in both, with mixed hearing loss in the one who survived. Microphthalmia and dysplastic/hypoplastic kidneys were detected in both, but with a variable degree of severity. Patient 1 had only an eye bud on the affected side, whereas patient 2 had small optic nerves more noticeable on one side. Severe dysplastic kidneys in patient 1 led to Potter sequence with early postnatal death and was associated with abnormal ureters and hypoplastic bladder and urethral orifice. Patient 2 was affected to a lesser degree and had unilateral agenesis of kidney, hypoplastic bladder, and vesicoureteral reflux of the present kidney. No renal dysfunction was detected clinically. Cryptorchidism was noted in both but could be physiologic in patient 1, who was born preterm. Other features that were noted in only one or the other half sib included abnormal umbilical artery, submucous cleft palate, agenesis of one testicle, and aganglionosis of the rectum and colon.

This syndrome has not been described previously. There are reports describing syndromes with aspects noted in our patients, and Table I lists those patients with the greatest similarities. The two sibs described by Goldberg and Shprintzen [1981]—although sharing brain anomalies, retardation of growth and mentality, cleft palate, and aganglionosis of the colon with our patients—had neither eye nor kidney malformations. This is also true for the patient described by Brunoni [1983]. Like our patients, the patients reported by Santos et al. [1988] had mental retardation, deafness, kidney anomalies, and Hirschsprung disease, but had no eye malformations, clefting, or skeletal involvement. Similarly, the patients described by Hurst et al. [1988] had brain malformations, eye anomalies, and aganglionosis of the colon as our patients did, but other findings in our patients were not noted in their report. All cited patients lacked the general alopecia and ectodermal dysplasia that are a major component of the complex anomalies seen in our patients. Ectodermal dysplasia syndromes (X-linked or autosomal dominant) are not included in the table because otherwise the similarity to our cases is very limited. Of special interest is the family described by Sanyanusin et al. [1995]. The individuals in this family had optic nerve colobomas, vesicoureteral reflux, and renal hypoplasia, but lacked brain malformations, clefting, skeletal anomalies, and abnormal ganglionic migration that are found in our patients. A mutation in the PAX2 gene was detected in the individuals of that pedigree, explaining the impaired embryonal development of the organs expressing this gene. Although several syndromes share manifestations with our patients, no single report has either a comparable combination of congenital anomalies or a similar magnitude of involvement as seen in our patients.

Possible mechanisms for this syndrome could include a submicroscopic contiguous gene deletion or mutation of a single paired box-containing (PAX) gene expressed in the primitive cells of the affected organs and involved in programming early development. Such a mutation could affect multiple structures that are related early in development but later lose their association [Redline et al., 1992]. In this case, it is plausible that the abnormal (or reduced) gene product may affect the regulation of other genes [Pierpont and Erickson, 1993] involved in central nervous system, eye, ear, ectoderm, kidney, ureter, myenteric plexus migration, vertebral segmentation, and testicular differentiation leading to the syndrome seen in our patients. A candidate gene could be sought on the X chromosome because the pattern of inheritance in these two half brothers strongly suggests an X-linked disorder.

REFERENCES

Brunoni D, Joffe R, Farah LMS, Cunha AJB (1983): Hirschsprung megacolon, cleft lip and palate, mental retardation and minor congenital malformations. J Clin Dysmorphol 1:20–22.

Goldberg RB, Shprintzen RJ (1981): Hirschsprung megacolon and cleft palate in two sibs. J Craniofac Genet Dev Biol 1:185–189.

Hurst JA, Markiewicz M, Kumar D, Brett EM (1988): Unknown syndrome: Hirschsprung's disease, microcephaly, and iris coloboma: A new syndrome of defective neuronal migration. J Med Genet 25: 494–497.

Pierpont JW, Erickson RP (1993): Invited Editorial: Facts on PAX. Am J Hum Genet 52:451–454.

Redline RW, Neish A, Holmes LB, Collins T (1992): Biology of disease. Homeobox genes and congenital malformations. Lab Invest 66: 659–670.

Santos H, Mateus J, Leal MJ (1988): Hirschsprung disease associated with polydactyly, unilateral renal agenesis, hypertelorism, and congenital deafness: A new autosomal recessive syndrome. J Med Genet 25:204–205.

Sanyanusin P, Schimmenti LA, McNoe LA, Ward TA, Pierpont MEM, Sullivan MJ, Dobyns WB, Eccles MR (1995): Mutation of the PAX 2 gene in a family with optic nerve colobomas, renal anomalies and vesicoureteral reflux. Nat Genet 9:358–363.